Remarks

Claims 1, 3-6, 8, 11-15 and 17-21 were pending in the subject application. Due to a restriction requirement, claims 15 and 17-21 have been withdrawn as non-elected subject matter. By this Amendment, the applicant has amended claim 1. Accordingly, claims 1, 3-6, 8 and 11-14 are now presented for consideration by the Examiner.

With regard to the Restriction Requirement, the applicants maintain their traversal for the reasons of record.

Support for the amendments set forth herein can be found throughout the subject specification including, for example, on page 3, line 33 and page 5, line 32 to page 6 line 2 (for "post-oestrus"); and Example 3 (for "live adult mammal"). The amendments to the claims have been made in an effort to lend greater clarity to the claimed subject matter and to expedite prosecution. These amendments should not be taken to indicate the applicant's agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein is earnestly solicited.

Claims 1, 3-5, 8 and 11-13 have been rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,734,398 or, in the alternative, under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 4,734,398 (the '398 patent is referred to hereinafter as "diZerega"). The applicant respectfully traverses this grounds for rejection because, as discussed in detail below and in the accompanying Expert Declarations, the diZerega reference does not disclose or suggest a material having the chemical properties or advantageous functional characteristics of the material claimed by the current applicant.

The material of the present invention (referred to below as "Micrin") differs from that of diZerega in four fundamental aspects:

1) it comes from different sources;
2) it is produced at a different time in the female reproductive cycle;
3) it is produced in response to different stimuli; and
4) it has different biological properties.

These four aspects will be reviewed in turn.

1. Sources of the Material

diZerega discloses "follicular regulating protein" (referred to below as FRP). From the diZerega experimental results it is clear that diZerega did not find FRP activity when using either peripheral blood or ovarian venous blood from the contralateral anovulatory ovary (see column 10 lines 52-57). Nor was there any FRP activity in the case of bilaterally anovulatory patients (see column 10 lines 57-60).

In contrast, as summarised in clause 7 of Dr. Hart's Declaration of 18 July 2003, Micrin is found in blood from either ovary, and is also detectable in bilaterally anovulatory individuals and in peripheral blood.

diZerega does not disclose such a material, nor could such a material be said to be "obvious" in view of the diZerega reference. There is no teaching in diZerega that would lead the skilled artisan to any other composition other than FRP, much less to the applicant's specific composition.

2. Time of Production of the Material

diZerega obtained FRP from blood taken "on days 12-14 after the onset of the last menstrual period", which corresponds to the pre-ovulatory phase (see column 8 lines 66-67 and column 9 lines 13-15)

In contrast, as summarised in clauses 7 and 8 of Dr. Hart's Declaration of 18 July 2003, Micrin is obtained on day 6 after oestrus in the sheep (see page 6 line 2 of the patent application), which is to say, post-ovulation.

This limitation of the applicant's claim is clearly not met by the diZerega reference nor does diZerega provide any suggestion that such a material may exist, or if it did exist, what characteristics (such as the ability to reduce organ mass) it would have.

3. Stimuli Eliciting Production of the Material

diZerega investigated the effect of clomiphene treatment on spontaneously menstruating women, the results being shown in figure 18, but neither of the results shown in the figure (follicular fluid protein activity and estradiol concentration) shows any significant difference between the untreated women and those treated with clomiphene. This shows that clomiphene does not induce FRP production.

In contrast, and as claimed by the current applicant, Micrin production is induced by clomiphene, post-oestrus. It should be emphasised that while clomiphene can induce ovulation in anovulatory female humans, there is no likelihood that acute administration of clomiphene would cause re-ovulation in a post-oestrus sheep. In this regard please refer to the accompanying Expert Declaration under 37 CFR §1.132 by Dr. Iain Clarke, a recognized expert in this field. Dr. Clarke states:

> [I]f sheep are provided with an acute administration of clomiphene within a few days after ovulation has occurred, as is described in the present patent application, this certainly does not cause further ovulation. The reproductive system is refractory to re-ovulation induction at this time, because the sheep would be in the luteal phase of the oestrous cycle, when progesterone levels are high; this prevents ovulation.

Thus, to the extent that the Office Action implies that Micrin production is the result of ovulation caused by clomiphene, this is clearly wrong. Micrin, as recited in the applicant's claims, can be obtained post-oestrus. This clearly differentiates micrin from FRP.

Dr. Clark goes on to observe "from my own immunohistochemistry experiments I have found that micrin can be found in brain tissues. This strongly suggests that that micrin is different from the compound described by diZerega."

4. Biological Properties

The Office Action has unfortunately incorrectly stated that diZerega's FRP "has the ability to reduce organ mass". It does not. diZerega used a bioassay that involved 23-day-old immature rats that were first subjected to hypophysectomy (i.e. removal of the pituitary gland). A well established effect of this surgical procedure is a reduction in ovarian mass, as is reported in Hart (1990). This effect is due to the absence of pituitary gonadotropins. After two days the rats were then treated with

varying concentrations of gonadotropins (such as hMG), and in some cases also with test solutions. The initial ovarian weight before injection was 21.2 mg, and the ovarian growth depended on the quantity of hMG supplied, that is to say hMG stimulated ovarian weight growth in a dose-dependent fashion, the maximum weight (for a single ovary) being 46 mg.

diZerega found that some test solutions inhibited or suppressed this stimulated ovarian regrowth. In particular diZerega found that the combined rat ovary weights for all the eluents gave values between 57 and 100 mg, while the elution peaks Ve/Vo = 1.42-1.55 from patient 1 inhibited the ovarian stimulation (the weight being 59 mg). Similarly the elution peaks Ve/Vo = 1.48-1.60 from patients 2 and 3 also suppressed the response of rat ovarian weight to hMG stimulation (57.4 mg as compared to 81.2 mg) [see column 9 lines 50-52 and column 9 lines 67-column 10 line 2; column 10 line 15-23; and column 10 lines 34-48 and lines 60-66].

Indeed, diZerega himself summarised the findings as: "In Examples One through Three protein(s) in ovarian venous effluent... inhibited rat ovarian weight gain in response to gonadotropin stimulation." [column 20 lines 29-33]. (emphasis added) Thus diZerega's FRP does not have the capability of reducing organ mass; it merely has the capability of inhibiting the increase of organ mass caused by the gonadotropins in the artificial situation of hypophysectomised rats.

The difference between reducing (losing) weight as opposed to inhibiting wait gain is critical to appreciate and relatively easy to understand. To illustrate: if my wife and I go on a vacation and I gain 5 pounds and my wife gains 10 pounds does this mean that I lost weight? Unfortunately, no. This simply means that I increased less. FRP, under specific conditions, results in less increase in organ mass. Conversely, the applicant's claims are drawn to a compound that causes a decrease in organ mass.

Micrin has been used to treat live adult animals, and has been found to produce an absolute decrease of mass in some body organs, including the ovaries. This is a very surprising property, and quite different to that of FRP, a local modulator of gonadotropin action. The ability to reduce organ mass is explicitly required by the applicant's claims; this characteristic is absent from the diZerega teachings.

Of course, for an anticipation rejection to be proper, a single prior art reference must disclose, within its four corners, each and every element of the claimed invention. In *Dewey & Almy Chem. Co. v. Mimex Co.*, Judge Learned Hand wrote:

> No doctrine of the patent law is better established than that a prior patent . . . to be an anticipation must bear within its four corners adequate directions for the practice [of the subsequent invention] . . . if the earlier disclosure offers no more than a starting point . . . if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation. 124 F.2d 986, 990; 52 USPQ 138 (2nd Cir. 1942).

The present invention is directed to an endogenous material inducible by clomiphene, that reduces organ mass, and which is obtained post-oestrus. Such a material is simply not disclosed, or even suggested, by diZerega. Because the diZerega reference does not disclose, within its four corners, a composition having the characteristics recited in the current claims, an anticipation rejection is improper.

The Office Action indicates that the unique properties of micrin are either found in diZerega or are so similar to the effects of FRP as to be "inherent" in diZerega. The applicant respectfully submits that no basis or justification for such speculation is available in diZerega.

Under the Patent Laws, a prior art rejection based on inherency is only proper if the prior art necessarily resulted in the claimed subject matter. *In re King*, 801 F2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). Further,

> the doctrine of inherency is available only when the prior inherent event can be established as a certainty. That an event may result from a given set of circumstances is not sufficient to establish anticipation....A prior inherent event cannot be established based on speculation, or where a doubt exists (emphasis added). *Ethyl Molded Product Co. v. Betts Package Inc.*, 9 USPQ2d 1001, 1032-33 (E.D. KY 1988).

In addressing this issue, Dr. Hart, another expert in the field, answers relevant questions as follows:

> 5. What if exogenous FRP were given to intact adult mammals, rather than hypophysectomised juvenile animals – would that cause an absolute reduction in ovarian mass? No, all this might achieve would be a blunting of the mid-cycle raise

in the mass of the ovulating ovary, given that the mode of action of FRP is to inhibit gonadotropin action. The potential suppression of a rise in mass of the ovulating ovary is not an absolute reduction in the mass of both ovaries, such as can be readily obtained with exogenous micrin.

6. Would the administration of exogenous FRP to adult intact mammals be expected to cause an abolsute reduction in non-gonadal organ masses, as is achieved with exogenous micrin? Again, no. To say otherwise would be to imply that gonadotropins increase the mass of non-gonadal organs, which is not the case, and ignores the fact that FRP does not even reduce in an absolute sense the mass of an ovulatory ovary; diZerega makes it clear (for example column 11, lines 55-66) that the effect of FRP is to suppress the response to gonadatropins.

As discussed above, it cannot reasonably be stated that the diZerega reference discloses or suggests a material that is obtained post-oestrus and that necessarily reduces organ mass. From a reading of diZerega, one skilled in the art would only expect FRP to impede gonadotropin-induced regrowth in ovaries. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102 is respectfully requested.

Nor is the subject invention obvious in view of diZereqa. Nothing in the diZerega reference would have led the skilled artisan to the advantageous materials and methods claimed by the current applicant. As noted above, apart from the molecular mass, no relevant physical or function similarities exist between the current applicant's material and the composition described in the diZerega reference. Certainly, diZerega's report of a 20 kD protein cannot make obvious every such protein that is subsequently discovered.

As the Examiner is undoubtedly aware, it is well established in the patent law that, in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must find both the suggestion of the claimed invention, and a reasonable expectation of success in making and practicing the invention, in light of the teachings of the prior art. *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1531, (Fed. Cir. 1988). The diZerega reference does not disclose or suggest the compounds claimed by the current applicant.

In view of the above, it should be clear that Micrin is not anticipated by diZerega, nor is it obvious in the light of this reference. Micrin is produced from a different source obtained at a different time during the menstrual cycle, and has the significantly different property of being able to

reduce organ size - these all go to show that the present invention is novel and nonobvious, and indeed surprising.

A finding of obviousness is proper only when the prior art contains a suggestion or teaching of the claimed invention. Here, it is only the applicant's disclosure that provides such a teaching, and the applicant's disclosure cannot be used to reconstruct the prior art for a rejection under 35 U.S.C. §103. This was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969):

> The Court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is we must review the prior art without reading into that art appellant's teachings. *In re Murray*, 46 CCPA 905, 268 F.2d 226, 112 USPQ 364 (1959); *In re Sprock*, 49 CCPA 1039, 301 F.2d 686, 133 USPQ 360 (1962). The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious. *In re Leonor*, 55 CCPA 1198, 395 F.2d 801, 158 USPQ 20 (1968). (Emphasis in original)

The diZerega reference does not disclose or suggest a material that is inducible by clomiphene nor does it disclose a material that can reduce organ mass. Rather, diZerega only provides FRP, a material that is not induced by clomiphene and only appears to affect ovaries in their response to gonadotropins.

Thus, the diZerega reference does not describe, teach, nor suggest a material having the unique characteristics of the claimed invention. As stated by Dr. Hart "FRP and micrin are demonstrably separate entities, having no connection whatsoever."

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §103 based on diZerega is respectfully requested.

In view of the foregoing remarks and the amendments above, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

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The applicant also invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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DRS/la

Attachment: Declaration Under 37 CFR §1.132 of Dr. Iain J. Clarke
Declaration Under 37 CFR §1.132 of Dr. John Ernest Hart